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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/657,076	09/09/2003	Mitsuhiro Ueno	UENO=8A	9181

1444 7590 05/04/2007

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EXAMINER	
GUZO, DAVID	

ART UNIT	PAPER NUMBER
1636	

MAIL DATE	DELIVERY MODE
05/04/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/657,076	UENO ET AL.	
	Examiner	Art Unit	
	David Guzo	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 February 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13-45* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

The Substitute Specification filed 2/12/07 is acceptable and has been entered.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 13-45 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

This rejection is maintained for reasons of record in the previous Office Action (mailed 10/12/06) and for reasons outlined below.

Applicants traverse this rejection by asserting that the state of the art prior to the instant invention taught clinically successful gene therapy using a retroviral vector. Applicants recite two articles published prior to the effective fining date of the instant invention and another published after the effective filing date of the instant invention, wherein applicants assert that said articles demonstrate successful gene therapy using retroviral vectors. Regarding unpredictability of the gene therapy art, applicants assert that gene therapy treatment methods should not be rejected as not complying with the enablement requirement because the treatment may result in undesirable side effects. Applicants assert that this is the purview of the FDA, not the Patent Office, and that

drugs which may result in side effects can be used in patients. Applicants assert that not all clinical studies using retroviral vectors have been put on hold and applicants cite post filing documents concerning how potential risks in using retroviral vectors can be avoided. Applicants assert that the benefits of using retroviral vectors outweighs the risks associated with said use and cite an article which teaches the risks and benefits of gene therapy for severe combined immunodeficiency in light of the leukemia-like disorder as a side effect. Applicants assert that the level of skill of the artisan in gene therapy is high and the problems outlined by the examiner could be easily overcome without undue experimentation based upon the guidance of the instant application and the knowledge in the art at the time of the instant invention.

Applicant's arguments filed 2/12/07 have been fully considered but they are not persuasive. With regard to applicants' arguments concerning the well developed state of the gene therapy art prior to applicants' invention, the Grossman et al. article describes the result of gene therapy for treatment of familial hypercholesterolaemia, using a retrovirus, in a **single patient** and Grossman et al. indicates that this represents the **first example** of stable correction of a therapeutic endpoint by gene therapy. The other reference cited by applicants (Malech et al.) recites prolonged expression (6 months) of $p47^{phox}$ CGD in patients. However, Malech et al. are extremely cautious in their interpretation of the results. For example, Malech et al. indicate that:

> **The clinical potential of gene therapy is yet to be realized** (emphasis added), and there has been considerable interest in defining both the scientific and clinical goals of human trials of gene transfer. In the case of CGD, where life-threatening infections may require many weeks or months of therapy and relapses are frequent, use of gene therapy to provide even short- to medium-term production of oxidase-positive autologous granulocytes ***may*** **be clinically beneficial** (emphasis added). p. 12138.

The reference cited by applicants that was published after the effective filing date of the instant invention cannot be used to establish the state of the art at or prior to the filing date of the instant invention. The two articles cited by applicants hardly establish that the gene therapy art was well developed, especially in view of the numerous articles cited by the examiner in the previous Office Action, wherein said articles describe the state of the art and unpredictability of the art. The instant claims recite gene therapy for any disease using any retroviral vectors and the two articles cited by applicants can hardly be considered to provide evidence of a state of the art so well developed that the skilled artisan could successfully treat any disease using any retroviral vector.

With regard to the unpredictability of the art, it is initially noted that applicants have not addressed the examiner's factual statements concerning the unpredictability of the gene therapy art and the numerous references cited by the examiner to support his arguments. Applicants concentrate their arguments on a portion of the rejection concerning the development of insertional mutagenesis and development of leukemia in several patients who were administered retroviral vectors for treatment of X-SCID or ADA-SCID. It is noted that the safety issue associated with administration of retroviral vectors is an issue which must be considered under 35 USC 112, 1st paragraph (how to make **and use** the claimed invention). If the skilled artisan would not be able to administer the vectors safely to patients, it is unclear how the claimed method would be enabled. Applicants' citation of articles and FDA guidelines which may minimize the risks of administering retroviral vectors were published **after** the effective filing date of

the instant invention and cannot be used to define the art at or before the claimed invention was made.

With regard to applicants' assertions that the gene therapy art was, at the time of applicants' invention, well developed and predictable and that the skilled artisan would not need to conduct undue experimentation in order to practice the claimed invention, the examiner cites additional references which document that even years after the effective filing date of applicants' invention, the gene therapy art continues to be poorly developed and unpredictable. Young et al. (J. Pathol., 2006, Vol. 208, pp. 299-318) notes that almost a decade after applicants' invention, the UK government expects to see the first licensed gene therapy medicines coming on stream **within 5 to 10 years**! It can hardly be considered that gene therapy was routine prior to applicants' invention when the current gene therapy research is so poorly developed that gene therapy medicines are not expected to appear for 5 to 10 more years (i.e. the years 2011 to 2016). Yi et al. (Current Gene Therapy, 2005, Vol. 5, pp. 25-35) notes that *ex vivo* gene therapy using retroviruses may in the future, after current problems are overcome, yield a successful outcome. Ellis et al. (Current Gene Therapy, 2005, Vol. 5, pp. 367-373) notes the problems associated with retrovirus silencing in stem cells and that re-design of the vectors themselves will be necessary to overcome this effect and allow efficient gene expression in transduced stem cells. It is noted that critical problems associated with successful practicing of gene therapy using retroviral vectors still need to be overcome many years after the effective filing date of applicants' invention and it must be concluded that the skilled artisan, at the time of said invention would have had to

have conducted undue and excessive experimentation, with no guidance from the instant application, to overcome the art recognized problems associated with gene therapy.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 14-20 and 43-45 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 14 (and dependent claims) are vague in that there is no antecedent basis for the term "the substrate" in claim 14.

No Claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Guzo, Ph.D., whose telephone number is (571) 272-0767. The examiner can normally be reached on Monday-Thursday from 8:00 AM to 5:30 PM. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

David Guzo
April 26, 2007

DAVID GUZO
PRIMARY EXAMINER

Notice of References Cited	Application/Control No. 10/657,076	Applicant(s)/Patent Under Reexamination UENO ET AL.	
	Examiner David Guzo	Art Unit 1636	Page 1 of 2

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
	A	US-			
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
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	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Young et al., J. Pathol., 2006, Vol. 208, pp. 299-318.
	V	Yi et al., Current Gene Therapy, 2005, Vol. 5, pp. 25-35.
	W	Ellis et al., Current Gene Therapy, 2005, Vol. 5, pp. 367-373.
*	X	Grossman et al., Nature Genetics, 1994, Vol. 6, pp. 335-341.

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.